Otolaryngology–Head and Neck Surgery (2007) 136, 563-567

ORIGINAL RESEARCH

Injectable hyaluronic acid for the correction of HIV-associated facial lipoatrophy

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OBJECTIVE: To evaluate the use of Perlane, an injectable form of hyaluronic acid, for the correction of HIV-associated facial lipoatrophy.

STUDY DESIGN AND SETTING: A prospective, observational study in a consecutive series of 18 HIV-positive males with facial lipoatrophy injected with Perlane. Fourteen patients were available for final analysis.

RESULTS: Mean follow-up time was 12 months. Based on photographic analysis, there was a significant early improvement ($P = 0.0035$). This difference remained significant after 12 months ($P = 0.04666$); no significant difference in grade was shown between 1 and 12 months ($P = 0.3693$). Office assessments of improvement showed an early marked improvement in 85.8% of patients, and 78.6% of subjects demonstrated at least moderate improvement at 12 months.

CONCLUSION/SIGNIFICANCE: Patient satisfaction was high, with only minor side effects and no late complications. Our findings support Perlane to be a feasible option for the provisional correction of mild to moderate facial lipoatrophy.

Newer treatment regimens used for human immunodeficiency virus (HIV) infection have led to the emergence of lipodystrophy syndrome (LDS). In addition to altered glycemic control and lipidemia, there is abnormal adipose regulation. Fat accumulation occurs in the abdomen, dorsocervical fat pad, and breast.[1] Concurrently there is a fat loss in the limbs, buttock, and face. Facial lipoatrophy is the most obvious and stigmatizing component of this syndrome. Its psychological effects on the patient can be profound and has led to patient noncompliance with medications.[2] The two classes of medications implicated with the development of lipoatrophy are protease inhibitors and nucleoside reverse transcriptase inhibitors (NRTIs). These medications comprise a commonly used treatment protocol known as highly active antiretroviral therapy (HAART). The evidence suggests that protease inhibitors alter production of cis-9-retinoic acid by inhibiting cytoplasmic retinoic acid binding protein type 1 (CRABP-1) as well as c-P450 3A.[3] This leads to decreased differentiation and increased apoptosis of peripheral adipocytes. Alternatively, NRTIs have been shown to inhibit mitochondrial DNA polymerase that leads to a depletion of mitochondrial DNA and increased adipocyte apoptosis.[4] Mallal et al[4] have also proposed a synergistic action of this combination of medications.

Medical strategies to correct LDS have not been shown to have any significant effect on facial lipoatrophy. Leptin replacement therapy is one of the latest treatments studied. Although insulin resistance, lipidemia, and central fat accumulation were reversible, there was no effect shown on facial atrophy.[5] This has led to the use of numerous injectable fillers as well as various surgical reconstructive options. Several procedures that involve free tissue transfer or synthetic implants have been documented for correction of facial contour deformities.[1,6-8] However, many patients are either not willing to undergo an invasive procedure or receive a more permanent injectable filling agent during their initial attempt at augmentation. Options in this category include silicone oil and Artecoll, which is a mixture of bovine collagen with polymethylmethacrylate beads. There is only limited literature that describes the use of these permanent filling agents for HIV-associated facial lipoatrophy.[9]

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Presented at the Annual Meeting of the American Academy of Otolaryngology–Head and Neck Surgery in New York, NY, September 20, 2004.

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0194-5998/$32.00
doi:10.1016/j.otohns.2006.11.049

Perlane (Q-Med, Sweden) is an injectable form of stabilized hyaluronic acid gel. It has been used in Europe for the correction of facial lipoatrophy for several years. However, few published trials that describe its use are available. We performed this study to objectively assess patient outcomes after injection of Perlane in patients with facial lipoatrophy. Secondary objectives were to document adverse reactions, describe patient satisfaction, and determine level of correlation between patient and physician outcome assessment.

Table 1
Preinjection grade of facial lipoatrophy

Grade	Number of Patients
I	6
II	5
III	3
IV	0
Total	14

PATIENTS AND METHODS

We evaluated 18 consecutive HIV-positive men, with a mean age of 47.2 years (range, 37 to 58 years), who presented with facial lipoatrophy. Patient recruitment was performed through direct physician referral or from an advertisement placed in a regional newspaper. Inclusion criteria were HIV-positive patients with clinically evident facial lipoatrophy and a history of antiretroviral use for at least 3 months. Exclusion criteria were patients who had undergone malar augmentation with a previous temporary filling agent in the past 2 years, a previous allergic reaction to hyaluronic acid, and patients unavailable for complete follow-up. An IRB is not available in our institution, but we obtained proper consent from the patients in keeping with the mandate of the Declaration of Helsinki. The study's aims, methods, source of funding, and all potential risks, burdens, and benefits to each patient were explained as part of the consent process. Each subject was informed of his right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. No potential subjects were found to be legally incompetent.

All 18 patients were injected after a combination of local and topical anaesthesia with 1% xylocaine without epinephrine and EMLA cream. Three vials or 2.1 cc of Perlane was injected per side into the submalar region. A single patient had only 2 vials injected per side due to cost constraints. The initial injection was placed into the basal layer of the immediate subdermis followed by the deep dermis with the use of the tunnelling technique.

Detailed facial assessment was performed that included baseline photography. There were no changes to the use of antiretroviral medications during the course of the study. At the initial consultation, all patients reported that their facial lipoatrophy had been stable for at least 12 months, and the mean duration since HIV seroconversion was 12.2 years. Patients were seen in follow-up regularly until 12 months postinjection. Four patients were unavailable for follow-up and were excluded leaving 14 patients for analysis. Complications were recorded. Facial assessment was made during each visit by both patient and physician; a 7-point Likert scale was used with a score of 7 representing dramatic improvement and 0 being no improvement. Photographs were taken at each office visit with standardized lighting, distance, and angles. Final photographic analysis was performed using the 4-stage facial lipoatrophy scale described by James et al.[10] Statistical analysis was done using the MedCalc software package.

RESULTS

Before injection, 11 of 14 patients presented with grade I or II facial lipoatrophy, with a mean grade of 1.79 as described

Figure 1 Grade I Lipoatrophy. **(A)** Preinjection; **(B)** 6-months' postinjection; **(C)** 12-months' postinjection.

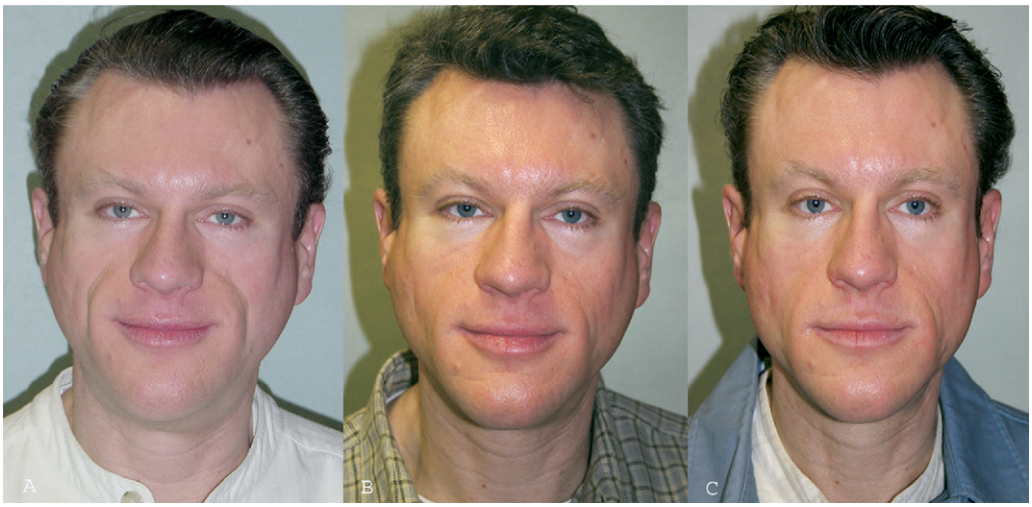

Figure 2 Grade II Lipoatrophy. **(A)** Preinjection; **(B)** 6-months' postinjection; **(C)** 12-months' postinjection.

in Table 1. Representative pre- and postinjection patient photographs are shown in Figures 1-3. After termination of the study, postoperative photographs were evaluated by the senior clinician and one of the coauthors (YT) who was blinded to the patient's identity. A weighted kappa value of 0.877 demonstrated a very high level of interobserver agreement. The evaluation performed by the blinded author is summarized in Figure 4. There was a statistically significant difference shown between pre- and early postinjection with the use of the Wilcoxin rank sum test for nonparametric unpaired data ($P = 0.0035$). During the time period of the study, patients did not deteriorate back to their preinjection levels of lipoatrophy. At the 12-month interval, there was still a slight statistical difference between the preinjection scores ($P = 0.0466$). No significant difference in grade was shown between the 1- and 12-month photographs ($P = 0.3693$).

Comparison of patient and physician scores from each office visit also correlated very well (weighted kappa = 0.858). The values were averaged at each time interval and presented in Figure 5. A gradual deterioration of product appeared to occur beginning at 6 months; 85.8% of patients had immediate marked improvement with their augmentation; 78.6% of patients showed at least moderate improvement after 12 months, which corroborates the photographic assessment. A single patient was dissatisfied with the results and claimed no improvement. He had grade III lipoatrophy and only received 1.4 cc of Perlane per side, which was insufficient for the severity of his lipoatrophy. Despite this, he improved by a single grade on photographic analysis and was rated as mild improvement by physician assessment.

The majority of patients tolerated the injections extremely well. Adverse events are summarized in Table 2. There was a total of 17 adverse reactions in 14 patients. No serious or late reactions were observed. Mean injection pain scores were 4.0 on a 10-point Likert scale. Only a single patient stated he would not undergo the procedure again because of the pain, and there was no lasting discomfort in

Figure 3 Grade III Lipoatrophy. **(A)** Preinjection; **(B)** 6-months' postinjection; **(C)** 12-months' postinjection.

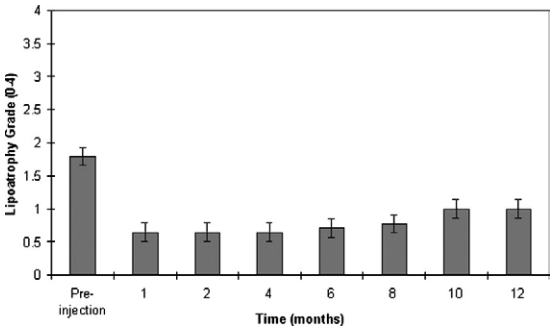

Figure 4 Photographic assessment of facial lipoatrophy. Mean grade pre- and postinjection ±1 SE.

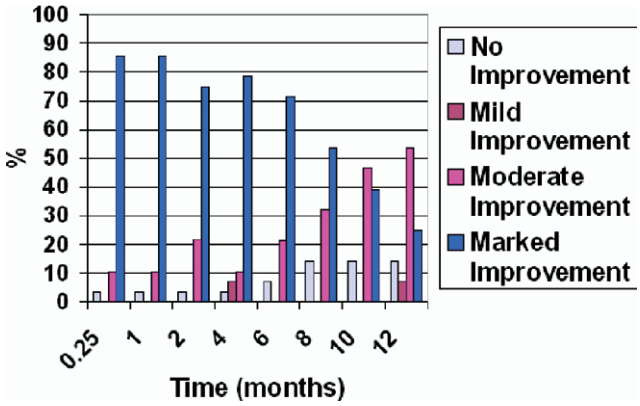

Figure 5 Postinjection lipoatrophy evaluation during each office visit. Combined mean physician and patient scores.

any patient beyond 1 month. One patient had prolonged palpability, erythema, and telangiectasia up to 4 months. He had undergone previous external beam radiation for oral Kaposi's sarcoma, which likely contributed to his increased morbidity with the injections.

DISCUSSION

There are many options for biodegradable injectable fillers, each with its own limitations. Products that contain bovine collagen (Zyplast) may not be desirable to some patients because of the risk of a hypersensitivity reaction that mandates prior skin testing.

Perlane is prepared by bacterial fermentation and therefore possesses a much lower rate of adverse reactions than do products that contain bovine collagen, which is reported as 3% to 5%.[11] Friedman et al[12] published international summary data that show a decline in the adverse reaction rate for injectable hyaluronic acid from 1 (0.15%) in 1400 patients in 1999 to 1 (0.06%) in 1800 patients in 2000. He suggested that most hypersensitivity reactions occur as a result of bacterial fermentation byproducts. In 2000, companies that produce hyaluronic acid gels began to use a more purified raw form of hyaluronic acid and this explains the drop in the rate of hypersensitivity reactions.

Lyophilized particulate human fascia lata (Fascian) prepared from sterilized human cadavers and micronized alloderm (Cymetra) have also been evaluated.[13-16] However, all of these products showed significant resorption from as early as 2 to 6 months. Polylactic acid (PLA, Sculptra, New-Fill) has been used extensively in Europe and Mexico for facial lipoatrophy.[17,18] The duration of this product is proposed to be 2 to 3 years mediated by an immediate volume replacement and a delayed proliferation of collagen fibers. It has been approved by the FDA in the United States since 2004.

One of the major criticisms of the use of hyaluronic acid gel in this patient population is the relative short duration of the product. Interestingly, we observed that over three-quarters of patients still had at least a moderate improvement at 12 months' postinjection. As well, photographic analysis still showed a small but significant difference from preinjection after 12 months. Furthermore, four patients still showed a marked improvement after 12 months. There were no changes to the patients' medications to account for these findings, although this may be a reflection of the small sample size. This suggests that the durability of Perlane in this patient population may be marginally longer than the 3 to 9 months commonly described.

It is important to note that all of the patients in our study had mild or moderate lipoatrophy. Except for one patient with grade II atrophy who had an exceptionally good result, all patients improved their postinjection scores by a single grade. In order to obtain complete correction in patients with more severe atrophy, more volume is required. Despite this, 86% of patients were felt to have a marked improvement in their appearance. Furthermore, the majority of patients expressed interest in receiving repeat injection after the termination of the study. Supplemental injections can be easily given that require lesser product than the initial treatment since product resorption was shown to be incomplete in most patients at the end of our study.

There were numerous patient factors identified during the course of the study that were felt to complicate the injection. Acne scarring and previous radiation to the facial

Table 2
Adverse events

Event	Number of Patients
Erythema beyond 1 week	4
Discomfort	4*
Palpability of product	4†
Telangiectasia	2
Ecchymosis	1
Oozing post-injection	1
Severe injection pain	1
Hypersensitivity reaction	0

*All lasted less than 1 month.
†All lasted less than 4 months.

soft tissues makes proper tissue level more difficult to determine. Large pores can leak filler during injection so injection needs to be deeper than usual. One patient with grade II atrophy was injected after previous malar implants. Although this patient was excluded because of incomplete follow-up, this may make the final result more unpredictable. Our early results with this patient, however, showed a marked improvement.

Another issue is the associated cost. At present there is no government or third-party insurer funding available to patients; this makes the procedure quite costly, especially when correcting the more severe forms of atrophy. This procedure should be viewed as reconstructive as opposed to cosmetic as it is a consequence of their illness and treatment. Although not specifically addressed in this study, the negative psychosocial impact of facial lipoatrophy has been well described.[2,19] Correcting this condition can have a dramatic positive impact on patients. One patient in our study stated that this procedure has "completely changed my life." Comments such as these reinforce the importance of exploring the various options of reconstruction for HIV-associated facial lipoatrophy.

CONCLUSION

Our findings indicate that Perlane is a feasible option for correction of facial lipoatrophy. The procedure was well tolerated without any long-term sequelae observed. Patients achieved a significant improvement in appearance lasting from up to 1 year.

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